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ORIGINAL ARTICLE

Prognostication in severe acute respiratory syndrome: A retrospective time-course analysis of 1312 laboratory-confirmed patients in Hong Kong

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Background and objective: The temporal importance of prognostic indicators for severe acute respiratory syndrome (SARS) has not been studied. This study identified the various clinical prognostic factors for SARS and described the temporal evolution of these factors in the course of the SARS illness in Hong Kong in 2003.

Methods: A retrospective analysis of the entire Hong Kong cohort of 1312 laboratory-confirmed SARS patients aged 15–74 years was undertaken. Demographic, clinical and laboratory data at presentation and investigative data during the first 10 days of illness from the time of symptom onset were compiled. Two adverse outcomes were examined: hospital mortality and the development of oxygenation failure based on the estimated PaO_2/FiO_2 ratio of <200 mm Hg. Logistic regression was used to identify the association between these prognostic factors and outcomes.

Results: Based on adjusted odds ratios with a *P*-value of <0.05, older age, male gender, elevated pulse rate and elevated neutrophil count were all predictive of oxygenation failure and death during the 10-day illness. Raised serum albumin and creatinine phosphokinase (CPK) levels were predictive of hospital mortality during this period. The presenting ALT and CPK level and the day 7 and day 10 platelet counts were predictive of oxygenation failure while the day 7 LDH was predictive of death. Contact exposure outside health-care institutions also appeared to carry higher risk of death.

Conclusion: This large-scale analysis identified important discriminatory parameters related to the patients' demographic profile (age and gender), severity of illness (pulse rate and neutrophil count), and multisystem derangement (platelet count, CPK, ALT and LDH), all of which prognosticated adverse outcomes during the SARS episode. While age, pulse rate and neutrophil count consistently remained significant prognosticators during the first 10 days of illness, the prognostic impact of other derangements was more time-course dependent. Clinicians should be aware of the time-course evolution of these prognosticators.

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INTRODUCTION

Severe acute respiratory syndrome (SARS) is a recently emerged infectious disease caused by a novel coronavirus. In 2003 it affected over 8000 patients worldwide with nearly 800 deaths, including 1755 infected patients and nearly 300 deaths in Hong Kong.[1] Over those few months, scientific knowledge and clinical experience with SARS grew rapidly, from initially making a diagnosis based on a constellation of clinical and epidemiological findings,[2] to one supported by laboratory confirmation.[3] The current World Health Organization (WHO) criteria for SARS comprise both clinical considerations and laboratory confirmation.[4]

Although much has been written on SARS prognostication[5–12] the studies are limited by their sample size, by the inclusion of patients based purely on clinical case definition[5,6] and by the use of early outcome indicator(s), such as the day 21 mortality[5–7] which might not represent the eventual outcome for the group. Prognosticators so far identified included: age, the most consistently found prognostic factor,[5–10,12] comorbidities,[6–8,12] admission tachycardia,[12] a high presenting neutrophil count,[5,9] LDH[9,10] and creatinine phosphokinase (CPK).[12] More extensive radiographic changes are also associated with adverse outcomes.[8,12–15] While previous studies largely agree on the prognostic role of age, comorbidities presenting tachycardia and presenting neutrophil count, the prognostic role of other clinical parameters such as LDH and CPK captured at various time-points in different studies[9,10,12] remains ill-defined.

The clinical data on all SARS patients in Hong Kong have been extensively captured by the Hospital Authority (HA), augmented by the e-SARS registry set-up during the SARS epidemic and the pre-existing computer-based clinical management system. This manuscript reports a retrospective analysis of the HA SARS database with the objective of describing the time-course evolution of the prognostic factors of SARS and exploring the temporal dynamics in SARS prognostication.

METHODS

Study population

The observational data of the entire cohort of 1312 laboratory-confirmed SARS patients aged 15–74 in Hong Kong were retrospectively analysed. These patients had been admitted into the 14 acute hospitals of the HA during the SARS outbreak; had been diagnosed as probable SARS based on the case definition of SARS issued by the HA on 19 March 2003;[†] and had retrospectively met the WHO criteria for laboratory-confirmed SARS.[3] Age was bounded for two reasons. The inclusion of a zero-mortality young age group in this analysis might diffuse the discriminatory power of the prognostic factors. The exclusion of the elderly group was to avoid the possible skewed influence of the non-aggressive treatment decision made at times by the care team in conjunction with the patient and/or patient's family. As this is a retrospective review of clinical information, in which the clinical investigators were blinded to the patients' confidential personal data, this study did not require informed consent.

Data collection and management

Data used in this analysis were amalgamated from four sources. The HA clinical management system provided data on demographics, admission and discharge, pharmacy records and laboratory results. Symptom onset dates, contact history and presenting symptoms were collected through a real-time case questionnaire conducted by the Hong Kong Government's Department of Health responsible for public health. Clinical data on comorbidities, daily vital signs and details of drugs, oxygen and ventilatory therapies were all manually abstracted from the medical records by clinical staff using a standardized data entry form for all hospitals. Comorbidities were defined to include COPD, cardiovascular disease, cerebrovascular accident, active cancer, diabetes mellitus, chronic renal insufficiency, and chronic liver disease. CXRs were retrospectively scored by 'blinded' radiologists in accordance with a 5-point scale for each of the six lung zones (zero for zero lung opacification, 1 for 1–25%, 2 for 26–50%, 3 for 51–75% and 4 for 76–100%), summating to a range of 0–24 score points.[15] Radiographic scorings were confined to five milestones: at presentation, commencement of ribavirin treatment if any, commencement of pulse

[†]The 19 March 2003 HA case definition of probable SARS required (i) the presence of new radiological infiltrates compatible with pneumonia; (ii) fever at or above 38°C; and (iii) the presence of at least two of the following: (a) chills; (b) new or increased cough; (c) new or increased shortness of breath; and (d) typical physical findings of consolidation. On 10 April 2003, part (iii) of the case definition was revised to include at least two of the following: (a) chills; (b) cough or breathing difficulty; (c) general malaise or myalgia; and (d) known history of exposure.

steroid treatment if any, peak lung opacification and prior to death/discharge. The presenting laboratory and radiological readings represented the first reading within 5 days of admission, or for inpatients with hospital-acquired SARS, of symptom onset; for studied time-points other than at presentation, the readings were chosen based on the following priority order: current day, 1 day before and 1 day after. This central database was intensively verified and cleaned by a team of clinical staff directly supervised by the authors. Where necessary, the clinical data were cross-checked with the in-charge clinician(s) and/or with the patients' medical records.

Selected time-points for study

'Days from symptom onset' has been used as the common reference point for profiling and analysing clinical and investigative data in order to eliminate the inter-patient differences in the timing of their presentation. 'Day 1' represents the first date on which SARS symptom(s) were experienced by the patients. The prognostic model analysed the risk associated with patient and clinical parameters at three time-points: at presentation and on days 7 and 10 from symptom onset. The clinical findings at presentation would be free from the effects of treatments such as the use of ribavirin and/or corticosteroid whereas analysis on day 7 and day 10 data would align all patients on a common time-course of the illness. Days 7 and 10 have been deliberately chosen with consideration given to: (i) the milestones of temporal disease progression in which day 7 marked the end of the first, viral replicative phase[16,17] and day 10 recorded the peak viral load;[7] (ii) minimization of contamination of data interpretation by drug treatments; and (iii) the balance between missing patients not yet admitted and missing those with an early onset of adverse outcome(s), as revealed by the timing of intubation.

Clinical management of SARS

While clinical decisions totally rested with the involved care team, the HA issued and updated clinical management guidelines on SARS based on evolving expert consensus primarily from the HA respiratory specialists and clinical microbiologists.[18,19] The treatment protocol on the prescription of antibiotics, ribavirin and corticosteroid has been described in several local studies.[10,20,21]

Adverse outcomes

All patients were retrospectively followed up until death or hospital discharge. Two adverse outcomes were studied: hospital mortality and oxygenation failure, the latter defined by a PaO_2/FiO_2 (P/F) ratio of less than 200 mm Hg (FiO_2 defined as the fraction of the inspired gas that was oxygen) a level defining the ARDS range of oxygenation impairment.[22] As the oxygen saturation level read by pulse oximetry (SpO_2) was more readily available at the bedside than the arterial oxygen tension (PaO_2), all PaO_2 levels used in our study were estimated from the SpO_2 readings based on the oxygen dissociation curve described by Severinghaus *et al.* in 1978.[23] An internal validation of the Severinghaus equation using our SARS cohort was performed and the results are shown in Figure 1.

Statistical analysis

Descriptive statistics including proportion, mean and SD for the entire cohort and each outcome group were compiled. Univariate analyses were performed to compare the differences in demographic, clinical and laboratory parameters between deceased and discharged patients. Patients who had reached the adverse outcome by the study time-points were

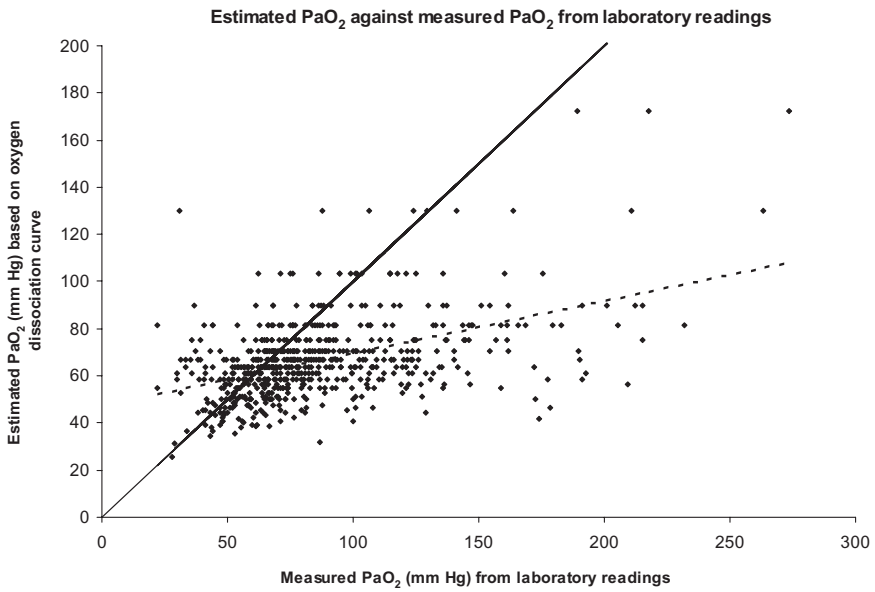

Figure 1 Results of an internal validation of the Severinghaus equation using 611 pairs of simultaneously measured oxygen saturation (by pulse oximetry—SpO_2) and PaO_2 values from 121 laboratory-confirmed SARS patients.

excluded from the analysis. Student's *t*-test was used for continuous variables and chi-squared test for categorical variables.

All variables with a *P*-value less than 0.25 based on univariate analysis were entered into multiple logistic regression models, with the exclusion of highly correlated clinical factors, respectively, using stepwise, forward and backward variable selection methods with entry and exit criteria of 0.05. A 'composite' model[24,25] for each of the three time-points was then developed utilizing all covariates selected in the above modelling algorithms plus any other variables identified in prior studies[5–10,12] as predictor variables of adverse outcome. The predictive performance of the 'composite' logistic regression model was evaluated on two criteria: discrimination and calibration. The discriminatory power of the model indicated by the area under the receiver operating characteristic curve was computed by the C-index.[26] The Hosmer–Lemeshow goodness-of-fit test[27] was performed to evaluate calibration, reflecting the degree of agreement between observed and expected adverse outcomes across different risk groups.

A two-sided *P*-value of less than 0.05 was considered to indicate statistical significance for all test statistics. All analyses were carried out using statistical analysis system (SAS) Version 8.2 software.

RESULTS

Patient selection

Of the 1755 SARS patients in Hong Kong, 1462 patients had laboratory confirmation of the diagnosis. Of these 1462 patients, 59 patients were aged less than 15 years and all survived; 91 patients were aged 75 years or above with a 58.2% mortality rate. Of the 53 deceased patients aged 75 years and above, 70% had comorbidities and 74% had not been cared for in the intensive care unit (ICU) before death, implying an overall conservative approach for elderly patients. Of the 1312 patients with laboratory-confirmed SARS aged 15–74 years, 1278 patients had the diagnosis confirmed by SARS coronavirus serology and the remaining 34 patients had the diagnosis confirmed by RT-PCR assays on clinical specimens obtained while alive and/or at post-mortem. More than four-fifths of the deceased patients had received ICU care.

Demographics and contact history (Table 1)

The mean age of the 1312 patients was 39.7 years (SD ±13.9). The male to female ratio was 2:3. Comorbidities were present in 11% of this study cohort. Healthcare facility-acquired SARS occurred in 49.9% of our cohort and community-acquired SARS in 40.7%. A complete epidemiological analysis for Hong Kong has been reported recently.[28]

Clinical presentation

The mean time between symptom onset and presentation to hospital was 4.4 days (SD ±2.7). Presenting symptoms included fever (93%), chills (61%), malaise (58%), myalgia (46%), rigor (38%), cough (41%), sputum (19%), shortness of breath (12%), diarrhoea (17%), nausea (12%) and vomiting (10%). CXR at presentation was abnormal in 83% of patients. Abnormal laboratory readings included reduced lymphocytes (62%), neutrophils (43%) and platelets (36%); raised LDH (47%), alanine aminotransferase (ALT) (22%), CPK (22%), activated partial-thromboplastin time (APTT) (26%) and international normalized ratio (5%). Oxygenation impairment was rare on presentation, with only 2% and 6%, respectively, falling into ARDS and acute lung injury ranges of estimated P/F ratio.[22]

Patient outcome and drug therapies

The ICU admission rate of the study cohort was 23%. Intubation and mechanical ventilation were administered to 13.8% of patients on a mean of 12.7 days (SD ±6.3) from symptom onset. While 27.1% had respiratory deterioration with estimated P/F ratio below 200 mm Hg, 40.8% required oxygen supplementation during hospitalization. The hospital mortality rate was 9.1%.

By day 7, ribavirin had been given to 79% of the admitted cohort for a mean duration of 3.5 days (SD ±1.7) and corticosteroids given to 74% for 3.2 days (SD ±1.6). By day 10, the corresponding figures were 91% of the admitted patients for 5.5 days (SD ±2.3) for ribavirin and 88% for 5.2 days (SD ±2.2) for corticosteroids. There were no differences in the ever-treated rates and duration between the deceased patients and survivors. Likewise there was no between-group difference in the cumulative dosages of ribavirin by days 7 and 10, respectively. The deceased group had a higher mean cumulative corticosteroid dosage than the survivors; by day 7 this was 5.3 g (hydrocortisone equivalent) versus 3.1 g ($P = 0.0002$) and by day 10 9.1 g versus 6.1 g ($P < 0.0001$).

Univariate analysis on hospital mortality (Tables 1,2)

On univariate analysis, age, gender, presence of comorbidities and contact exposure were strongly associated with hospital mortality. The deceased group was more likely to have afebrile presenting symptom and ongoing (from presentation to day 10) advanced radiographic changes. Statistically significant laboratory readings at presentation included raised WCC, neutrophil count, blood urea, serum glucose, creatinine, bilirubin, CPK, LDH, CRP and reduced Hb and albumin. As opposed to the findings from earlier studies,[7,29] there was no association between hepatitis B antigen and mortality ($P = 0.70$) in SARS patients. The findings of the at-presentation model largely persisted onto day 7 and day 10 models.

Table 1 Demographics and contact history in 1312 patients with laboratory-confirmed SARS

	Overall ($n = 1312$)	Deceased ($n = 119$)	Survivor ($n = 1193$)	P-value
Age				
Mean ± SD	39.7 ± 13.9	54.8 ± 13.3	38.2 ± 13.1	<0.0001
Median	38	55	36	
Range	15–74	28–74	15–74	
Gender				
Female	785 (59.8%)	54 (45.4%)	731 (61.3%)	0.0007
Male	527 (40.2%)	65 (54.6%)	462 (38.7%)	
Comorbidity				
Nil	1167 (88.9%)	71 (59.7%)	1096 (91.9%)	<0.0001
Any	144 (11.0%)	48 (40.3%)	96 (8.1%)	
COPD	1 (0.7%)	0 (0.0%)	1 (0.1%)	—
Cancer	14 (9.7%)	3 (2.5%)	11 (0.9%)	0.1269
Cerebrovascular disease	27 (18.8%)	9 (7.6%)	18 (1.5%)	<0.0001
Ischaemic heart disease	47 (32.6%)	18 (15.1%)	29 (2.4%)	<0.0001
Diabetes mellitus	72 (50.0%)	25 (21.0%)	47 (3.9%)	<0.0001
Chronic renal failure/insufficiency	22 (15.3%)	10 (8.4%)	12 (1.0%)	<0.0001
Chronic liver disease	6 (4.2%)	5 (4.2%)	1 (0.1%)	<0.0001
SARS contact source				
Amoy Gardens Apartments and related	375 (28.6%)	35 (29.4%)	340 (28.5%)	<0.0001
Non-Amoy Gardens Apartments community acquired	159 (12.1%)	24 (20.2%)	135 (11.3%)	
Institution (health-care workers)	379 (28.9%)	8 (6.7%)	371 (31.1%)	
Institution (patients or visitors)	275 (21.0%)	39 (32.8%)	236 (19.8%)	
Airflight/imported	66 (5.0%)	7 (5.9%)	59 (4.9%)	
Unknown/missing	58 (4.4%)	6 (5.0%)	52 (4.4%)	
Health-care workers				
Doctors	61 (16.1%)	4 (50.0%)	57 (15.4%)	<0.0001
Nurses	195 (51.5%)	1 (12.5%)	194 (52.3%)	
Health care assistants	48 (12.7%)	2 (25.0%)	46 (12.4%)	
Medical students	16 (4.2%)	0 (0.0%)	16 (4.3%)	
Others[†]	59 (15.6%)	1 (12.5%)	58 (15.6%)	

[†]Include allied health, clerical, technical and other staff working in health-care institutions.

Multivariate analysis on hospital mortality (Table 3)

Under multiple logistic regression, age was consistently the most significant risk factor for hospital mortality at presentation, and on days 7 and 10 (each with $P < 0.0001$). The increased risk in males was significant ($P = 0.01$) at presentation only. The nature of contact exposure played a weak but significant prognostic role on day 7 only, with the Amoy Gardens Apartments-related cohort as well as non-Amoy Gardens Apartments community-acquired cohort having a greater risk of mortality in comparison to health-care workers who acquired the disease inside health-care institutions ($P = 0.008$ and 0.04, respectively). However, there was no significant difference in risk when the reference health-care worker group was compared with those patients/visitors who similarly acquired SARS inside health-care institutions; to those who acquired SARS from community sources other than the Amoy Gardens Apartments and to those who acquired SARS from air-flight or outside Hong Kong.

Among the clinical parameters, the presenting neutrophil count ($P = 0.0002$) and pulse rate ($P = 0.0003$) were highly significant prognostic indicators of hospital mortality. The pulse rate re-emerged as significant on day 10 ($P = 0.01$). Serum albumin emerged on day 7 ($P = 0.0003$) and day 10 ($P = 0.006$) as a significant prognostic indicator. Interestingly, serum CPK was a significant prognosticator both at presentation ($P = 0.002$) and on day 10 ($P = 0.03$). Despite attention given in earlier reports,[5,9,10] the significance of serum LDH as a predictor of mortality was only marginally established on day 7 ($P = 0.03$). Radiographic progression was significant on day 10 only ($P = 0.006$).

Multivariate analysis on oxygenation failure (Table 4)

Using multiple logistic regression, the significant factors predicting oxygenation failure, despite slight differences in the odds ratios and P-values, were quite similar to the factors predicting hospital mortality, except that ALT ($P = 0.002$ at presentation), neutrophil count ($P < 0.0001$ on days 7 and 10), platelet count ($P = 0.0008$ on day 7 and 0.0004 on day 10) and pulse rate ($P = 0.01$ on day 7) were additionally identified as prognosticators, while albumin no longer played a

Table 2 Univariate analysis on the association of prognostic factors with hospital mortality

	At presentation				
	Deceased		Survivor		
Clinical signs	*n*	Mean ± SD/ % of total	*n*	Mean ± SD/ % of total	*P*-value
Temperature (peak)					
<38°C	34	28.8%	245	20.6%	
≥38°C	84	71.2%	942	79.4%	0.0389*
Pulse (at peak temperature)	117	99.9 ± 18.1	1187	98.8 ± 14.7	0.5442
Respiratory rate (peak)	82	21.6 ± 7.0	653	20.2 ± 5.6	0.0706
Bowel open					
Normal (<3)	63	80.8%	531	81.6%	
With diarrhoea (≥3)	15	19.2%	120	18.4%	0.8639
PaO_2/FiO_2 ratio (mm Hg)					
<200	12	10.4%	17	1.5%	
200–299	21	18.3%	58	5.0%	
300–399	59	51.3%	559	48.1%	
400+	23	20.0%	527	45.4%	<0.0001***
X-ray score					
0	8	8.1%	194	17.9%	
1–9	76	76.8%	840	77.3%	
10–19	12	12.1%	48	4.4%	
20–24	3	3.0%	4	0.4%	0.0001***
Laboratory readings					
WCC (10^9/L)	118	7.60 ± 4.52	1192	5.56 ± 2.15	<0.0001***
Neutrophil count (10^9/L)	118	5.96 ± 3.89	1192	4.12 ± 2.02	<0.0001***
Lymphocyte count (10^9/L)	118	0.94 ± 0.58	1192	0.93 ± 0.46	0.8664
Hb (g/dL)	118	12.76 ± 2.18	1192	13.30 ± 1.59	0.0103*
Platelet count (10^9/L)	118	182.05 ± 90.12	1192	177.14 ± 61.79	0.5638
International normalized ratio	82	1.22 ± 0.83	910	1.05 ± 0.18	0.0630
Prothrombin time (s)	82	13.36 ± 8.83	910	11.56 ± 2.30	0.0697
Activated partial-thromboplastin time (s)	81	39.27 ± 13.90	903	36.61 ± 7.31	0.0917
Glucose, Random (mmol/L)	64	8.72 ± 5.08	524	6.68 ± 2.49	0.0024**
CRP (mg/L)	43	81.10 ± 72.11	621	35.18 ± 44.11	0.0002***
Albumin (g/L)	115	35.95 ± 5.50	1161	39.79 ± 4.54	<0.0001***
Globulin (g/L)	100	34.35 ± 6.08	931	33.79 ± 4.74	0.3693
Blood urea (mmol/L)	117	6.87 ± 6.97	1191	4.02 ± 3.07	<0.0001***
Creatinine (as times of upper normal reference) excludes chronic renal failure/insufficiency	107	0.88 ± 0.24	1178	0.77 ± 0.20	<0.0001***
Bilirubin, Total (umol/L)	115	13.00 ± 27.10	1161	7.77 ± 6.36	0.0410*
ALP (as times of upper normal reference)	115	0.79 ± 1.13	1161	0.62 ± 0.34	0.1036
ALT (as times of upper normal reference)	115	1.23 ± 2.32	1161	0.86 ± 1.23	0.0921
CPK (as times of upper normal reference)	109	1.93 ± 2.97	1120	0.90 ± 1.62	0.0005***
LDH (as times of upper normal reference)	95	1.55 ± 1.03	1030	1.14 ± 0.60	0.0003***
Hepatitis B antigen					
Positive	9	10.0%	89	8.8%	
Negative	81	90.0%	922	91.2%	0.7024

*P-value < 0.05, **P-value < 0.01, ***P-value < 0.001.

†Patients who died on or before days 7 and 10 were excluded from analysis for days 7 and 10, respectively.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; CPK, creatinine phosphokinase.

significant prognostic role in oxygenation failure. The day 10 contact history was a significant prognosticator: the Amoy Gardens Apartments-related ($P = 0.04$), the non-Amoy Gardens Apartments community-acquired cohort ($P = 0.02$) together with the cohort acquiring SARS from air-flight or outside Hong Kong ($P = 0.01$) had a higher risk in comparison to the reference cohort of health-care workers who acquired the disease inside health-care institutions. The health-care workers did not differ in risk from the other health-care institution-infected subgroup of patients/visitors.

The above analysis on oxygen failure was conducted without including radiological parameters as

Day 7					Day 10				
Deceased†		Survivor			Deceased†		Survivor		
n	Mean ± SD/ % of total	*n*	Mean ± SD/ % of total	*P*-value	*n*	Mean ± SD/ % total	*n*	Mean ± SD/ % total	*P*-value
56	56.6%	646	62.2%		87	78%	878	76%	
43	43.4%	393	37.8%	0.2726	24	22%	277	24%	0.5768
97	88.8 ± 17.7	1040	84.9 ± 15.3	0.0404*	111	86.9 ± 18.3	1152	80.8 ± 15.8	0.0009**
68	22.7 ± 7.6	525	20.0 ± 5.5	0.0062**	81	24.3 ± 7.6	574	21.1 ± 7.1	0.0002***
40	76.9%	390	73.4%		44	70%	450	72%	
12	23.1%	141	26.6%	0.5865	19	30%	172	28%	0.6725
22	22.7%	28	2.8%		55	52%	80	7%	
21	21.6%	72	7.1%		26	25%	135	12%	
40	41.2%	484	47.8%		20	19%	517	46%	
14	14.4%	428	42.3%	<0.0001***	4	4%	390	35%	<0.0001***
2	3.3%	52	7.4%		1	2%	25	4%	
39	63.9%	587	83.0%		22	47%	510	78%	
13	21.3%	62	8.8%		15	32%	113	17%	
7	11.5%	6	0.8%	<0.0001***	9	19%	10	2%	<0.0001***
99	10.15 ± 5.29	1019	7.74 ± 4.08	<0.0001***	109	13.20 ± 5.13	1130	11.47 ± 5.41	0.0015**
97	8.87 ± 4.98	1014	6.45 ± 3.99	<0.0001***	107	12.05 ± 4.93	1128	10.28 ± 5.39	0.0012**
97	0.55 ± 0.28	1014	0.68 ± 0.31	0.0002***	107	0.45 ± 0.25	1128	0.58 ± 0.32	<0.0001***
99	12.04 ± 2.05	1019	12.62 ± 1.56	0.0066**	109	11.68 ± 1.83	1130	12.36 ± 1.58	0.0003***
99	165.00 ± 74.32	1018	165.49 ± 62.27	0.9494	109	187.03 ± 71.85	1130	207.22 ± 79.32	0.0107*
53	1.45 ± 1.16	474	1.11 ± 0.59	0.0413*	65	1.47 ± 1.43	485	1.10 ± 0.40	0.0388*
53	15.58 ± 12.21	474	11.84 ± 6.25	0.0324*	65	15.98 ± 15.10	485	11.65 ± 4.42	0.0246*
53	44.36 ± 24.62	476	38.59 ± 10.67	0.0970	65	36.11 ± 13.96	482	35.17 ± 9.30	0.6010
41	11.50 ± 4.46	316	8.61 ± 3.42	0.0002***	54	11.63 ± 5.32	394	9.19 ± 3.35	0.0017**
29	94.90 ± 75.46	308	38.11 ± 44.92	0.0004***	36	65.01 ± 48.02	316	53.38 ± 57.57	0.2442
91	30.32 ± 5.66	840	35.38 ± 4.41	<0.0001***	100	27.59 ± 5.01	901	33.13 ± 4.61	<0.0001***
79	33.50 ± 5.80	615	33.09 ± 4.66	0.5506	88	31.15 ± 5.69	643	32.14 ± 4.89	0.1233
98	8.30 ± 6.67	991	4.70 ± 3.55	<0.0001***	108	9.00 ± 6.26	1110	5.28 ± 3.50	<0.0001***
91	0.87 ± 0.27	979	0.75 ± 0.19	<0.0001***	102	0.84 ± 0.36	1098	0.71 ± 0.22	0.0003***
91	18.12 ± 21.20	840	10.81 ± 9.52	0.0016**	100	22.31 ± 17.74	901	16.54 ± 13.86	0.0021**
91	0.72 ± 0.71	839	0.60 ± 0.35	0.1105	100	0.76 ± 0.70	901	0.65 ± 0.40	0.1110
91	1.32 ± 1.07	840	1.19 ± 1.45	0.2873	100	1.38 ± 1.13	901	1.63 ± 1.84	0.0529
76	2.12 ± 3.97	695	0.86 ± 1.25	0.0074**	74	1.30 ± 2.19	703	0.73 ± 1.24	0.0301*
63	1.96 ± 1.04	633	1.36 ± 0.83	<0.0001***	72	2.20 ± 1.03	621	1.57 ± 0.93	<0.0001***

they were highly correlated. When the analysis was repeated with the inclusion of radiological parameters on a subset of study subjects with available radiological data, the same consistent set of independent prognostic factors, except for insignificant presenting CPK, day 7 platelet count and day 10 SARS exposure history were largely observed. As expected, the radiological scores were found to be a highly significant prognosticator at all studied time-points ($P < 0.0001$ at presentation and day 10, $P = 0.01$ on day 7).

Predictive performance (Tables 3,4)

In comparing the predictive performance between the two sets of outcome models, the mortality models

Table 3 Multiple logistic regression (composite model) on the association of risk and prognostic factors with hospital mortality

	At presentation ($n = 1095$) Deceased: 94 Survivor: 1001			Day 7 ($n = 673$) Deceased: 62† Survivor: 611			Day 10 ($n = 408$) Deceased: 29† Survivor: 379		
	Adjusted OR	(95% CI)	*P*-value	Adjusted OR	(95% CI)	*P*-value	Adjusted OR	(95% CI)	*P*-value
Age (per 10 years increase)	2.16	(1.76–2.63)	<0.0001***	1.81	(1.44–2.27)	<0.0001***	2.09	(1.45–3.03)	<0.0001***
Gender (M vs F)	2.04	(1.18–3.52)	0.0104*						
Contact source (air flight/imported vs Hosp:HCW)				2.10	(0.50–8.86)	0.3117			
(Amoy Gardens Apartments and related vs Hosp:HCW)				4.65	(1.51–14.35)	0.0075**			
(Hosp: non-HCW vs Hosp:HCW)				1.50	(0.44–5.16)	0.5208			
(Non-Amoy Gardens Apartments community vs Hosp:HCW)				3.73	(1.07–12.99)	0.0386*			
Pulse (per 10/minute increase)	1.35	(1.15–1.59)	0.0003***				1.40	(1.08–1.82)	0.0118*
CXR score (per score increase)							1.12	(1.03–1.21)	0.0056**
Neutrophil (per 10^9/L increase)	1.19	(1.09–1.30)	0.0002***						
Hb (per g/L increase)	0.89	(0.77–1.03)	0.1218						
Albumin (per g/L increase)	0.96	(0.91–1.02)	0.1826	0.89	(0.84–0.95)	0.0003***	0.86	(0.77–0.96)	0.0060**
Alanine aminotransferase (as times of upper normal reference)	1.16	(0.96–1.40)	0.1386						
Creatinine phosphokinase (as times of upper normal reference)	1.18	(1.06–1.31)	0.0022**				1.27	(1.03–1.56)	0.0251*
LDH (as times of upper normal reference)	1.06	(0.77–1.47)	0.7119	1.33	(1.03–1.73)	0.0292*	0.90	(0.54–1.50)	0.6913
C-index (area under ROC curve)	0.862			0.848			0.899		
Hosmer–Lemeshow goodness-of-fit test (*P*-value)	0.6359			0.1289			0.1373		

*P-value < 0.05, **P-value < 0.01, ***P-value < 0.001.

†Patients who died on or before days 7 and 10 were excluded from analysis for days 7 and 10, respectively.

F, female; M, male; HCW, all clinical and non-clinical staff working in healthcare institutions; ROC, receiver operating characteristic.

Table 4 Multiple logistic regression (composite model) on the association of risk and prognostic factors with oxygenation failure

	At presentation ($n = 1179$) Ever with OF†: 309‡ No OF†: 870			Day 7 ($n = 855$) Ever with OF†: 197‡ No OF†: 658			Day 10 ($n = 840$) Ever with OF†: 147‡ No OF†: 693		
	Adjusted OR	(95% CI)	*P*-value	Adjusted OR	(95% CI)	*P*-value	Adjusted OR	(95% CI)	*P*-value
Age (per 10 years increase)	1.61	(1.43–1.81)	<0.0001***	1.49	(1.30–1.72)	<0.0001***	1.44	(1.24–1.68)	<0.0001***
Gender (M vs F)	1.42	(1.05–1.90)	0.0207*	1.44	(1.01–2.06)	0.0434*			
Contact source (air flight/imported vs Hosp:HCW)				1.53	(0.78–2.99)	0.2159	2.63	(1.31–5.29)	0.0067**
(Amoy Gardens Apartments and related vs Hosp:HCW)				1.43	(0.89–2.30)	0.1438	1.75	(1.03–2.99)	0.0386*
(Hosp: non-HCW vs Hosp:HCW)				0.85	(0.49–1.47)	0.5601	1.31	(0.72–2.38)	0.3697
(Non-Amoy Gardens Apartments community vs Hosp:HCW)				1.40	(0.75–2.62)	0.2985	2.12	(1.13–3.98)	0.0199*
Temperature (>38°C vs ≤38°C)				1.45	(0.96–2.17)	0.0749			
Pulse (per 10/min increase)	1.19	(1.08–1.32)	0.0006***	1.18	(1.04–1.35)	0.0106*	1.25	(1.10–1.42)	0.0006***
Neutrophil (per 10^9/L increase)	1.25	(1.17–1.34)	<0.0001***	1.17	(1.11–1.23)	<0.0001***	1.10	(1.06–1.14)	<0.0001***
Platelet (per 10^9/L increase)				0.94	(0.90–0.97)	0.0008***	0.95	(0.92–0.98)	0.0004***
Albumin (per g/L increase)	0.97	(0.94–1.01)	0.1119	0.97	(0.93–1.02)	0.2375	0.98	(0.93–1.03)	0.352
Alanine aminotransferase (as times of upper normal reference)	1.18	(1.06–1.31)	0.002**	1.12	(1.00–1.25)	0.0612			
Creatinine phosphokinase (as times of upper normal reference)	1.11	(1.02–1.21)	0.0175*						
C-index (area under ROC curve)	0.766			0.766			0.744		
Hosmer–Lemeshow goodness-of-fit test (*P*-value)	0.0673			0.1066			0.8854		

*P-value < 0.05, **P-value < 0.01, ***P-value < 0.001.

†OF, Oxygenation failure (PaO_2/FiO_2 ratio <200 mm Hg).

‡Patients with OF on presentation or day 1, on or before days 7 and 10 were excluded from analysis for at-presentation, days 7 and 10, respectively.

F, female; M, male; HCW, all clinical and non-clinical staff working in healthcare institutions; ROC, receiver operating characteristic.

at the three time-points were slightly better than the oxygenation failure models on both discrimination and calibration. Judged by the C-index (i.e. area under receiver operating characteristic curve), the mortality models for the three time-points indicated a fairly strong discriminatory power (0.86, 0.85 and 0.90, respectively) compared with the oxygenation failure models (0.77, 0.77 and 0.74, respectively). Similarly, given that the *P*-value of the Hosmer–Lemeshow test did not indicate a lack of fit for the six models (all with $P > 0.05$), the mortality models showed a better model fit than the counterparts except for the day 10 oxygenation failure model, which showed the best model fit ($P = 0.86$).

DISCUSSION

This study, utilizing the demographic, epidemiological and serial bedside and laboratory findings of the entire Hong Kong cohort of laboratory-confirmed SARS patients aged 15–74 years, provides the most thorough analysis to date on SARS prognostication. While confirming the prognostic significance of age, and the presenting pulse rate and neutrophil count as described in earlier studies,[5–10,12,30] this study further shows that age, pulse rate, and neutrophil count remained predictive of two different adverse outcomes, namely death and the development of oxygenation failure, throughout the first 10 days of illness.

The role of LDH and CPK in SARS prognostication has been further delineated using a time-course approach and factoring in the batch-to-batch variation in the LDH laboratory reference range. Day 7 LDH, but not presenting or day 10 LDH, was a significant prognosticator of death but not of oxygenation failure. In another earlier study, the high LDH found in SARS patients had been attributed to the release of LDH isoenzyme 1 (LD1) by blood erythrocytes rather than by the myocardium.[11] Although one could postulate that lysis of blood erythrocytes was the major process contributing to a high LDH level on day 7, we were unable to identify a parallel decrease in Hb. This study further confirmed that the presenting CPK is an important predictor of oxygenation failure and death, and also that the presenting ALT is a newly found prognosticator of oxygenation failure. By day 10, CPK predicted death but not oxygenation failure. All in all, at the onset of illness there appeared to be tissue injury in the liver and muscles in parallel with lung injury, and the extent of muscle injury not only predicted lung injury, but also impacted on death. By day 10, in those patients spared oxygenation failure, ongoing non-lung tissue injuries, as reflected by LDH and CPK, impacted on survival.

This unique description of the temporal evolution of prognosticators over the first 10 days of illness provides insights into yet another evolving process which contributed to mortality. By days 7–10 of illness, serum albumin became predictive of death, but not of oxygenation failure. In other words, patients spared oxygenation failure might still die if they demonstrated poor nutritional/metabolic state (as reflected by the serum albumin). Interestingly, the serum albumin in this analysis might have served as a surrogate marker for 'the presence of comorbidities', a variable well described in other studies as a prognosticator.[6,8,12]

While prognostic factors may simply serve as severity or surrogate markers of the viral insult and/or host response, the possible pathogenic role of platelets needs to be considered. This study showed thrombocytopaenia in 36% and deranged APTT in 26% of the cohort on presentation; the former seen in 40% in the Vietnamese cohort[31] and the latter in 42.8% of Yang's cohort.[32] Based on the finding of an elevated D-dimer in 45%[5] and of disseminated intravascular coagulopathy in 2.5%[33] of a smaller Hong Kong cohort, the mechanism of the observed thrombocytopaenia is likely to be consumptive in nature. Both this study and the Vietnamese study[31] have shown that the platelet and APTT abnormalities observed during the first week of illness were usually transient. The finding of thrombocytopaenia persisting to days 7 and 10 being predictive of oxygenation failure but not of death may implicate platelet aggregation and consumptive coagulopathy in the pathogenesis of acute lung injury in SARS. While ongoing endothelial damage from infection, oxygen therapy and artificial ventilation has been postulated as the mechanism for platelet fragmentation and consumption,[32] our time-course analysis shows that thrombocytopaenia observed as early as days 7 and 10 (before intubation), was associated with eventual lung failure. Thrombocytopaenia observed during this stage of SARS is unlikely to be iatrogenic and is more likely to be a virally mediated systemic inflammatory response. The reported elevation of certain pro-inflammatory cytokines in the acute illness[34,35] further supports a heightened role of inflammation in the pathogenesis of SARS.

The prognostic significance of the neutrophil count on days 7 and 10 must be interpreted with caution, as the day 7 and day 10 neutrophil readings would have been influenced by the use of corticosteroids at that time. The possible interactive effects between particular clinical parameters and corticosteroid usage prompted the investigators to leave corticosteroid usage out of this analysis.

The prognostic effect of contact history is unexpected. Theoretically, contact history could be considered a crude measure of the infective viral dose the patient had been exposed to, which, in turn, is the composite end-point of the interplay in infection control practices between the host and environment. Health-care facility-acquired infection had a significantly lower mortality risk than community-acquired infection, perhaps due to a difference in the degree of environmental contamination between the health-care facility and a specific community, or to a difference in the nature, especially the duration and repetitiveness, of exposure to the infectious pathogen. Despite the current finding of a lack of difference in outcome between hospitalized patients and health-care workers, much more detailed epidemiological study is required to understand the impact on the infective viral dose of specific

environmental exposure, and of variations in personal infection control measures such as hand washing and use of personal protective gear.

This large-scale analysis identifies important discriminatory parameters related to the patients' demographic profile (age), to the patients' severity of illness (pulse rate and neutrophil count), and to the patients' multisystem derangement (platelet count, CPK, ALT and LDH), all of which prognosticated adverse outcomes during the SARS episode. While age, pulse rate and neutrophil count consistently remained significant prognosticators during the first 10 days of the illness, the prognostic impact of the system-based derangement was more time-course dependent. Clinicians should be aware of the time-course evolution of respective prognosticators.

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